BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

Claims 35 and 38 have been amended to properly claim the invention. Claim 40 correctly names the ORL_1 receptor as opioid receptor-like 1, and Claims 35 and 38 have been amended to correctly name the receptor. No new matter has been added herewith.

The changes made to the claims by the current amendment, including **[deletions]** and additions, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment.

Rejection under 35 U.S.C. §112, first paragraph

Claims 35-36, 38 and 47 have been rejected under 35 U.S.C. §112, first paragraph with regard to the recitation of an isolated peptide encoded by a polynucleotide which corresponds to at least 70% or 90% of SEQ ID NO: 1 or its complimentary strand. The Examiner believes that there is insufficient guidance as to which amino acids may be altered while still maintaining peptide function as a ligand of ORL_1.

However, the specification provides several examples of an isolated peptide encoded by a polynucleotide which corresponds to at least 70% or 90% of SEQ ID NO: 1 or its complimentary strand. The description of Figure 7 (p. 9, lines 21-24) reveals the prepronociceptin gene (PPNOC) encoded by SEQ ID NO: 1 as well as comparisons "between translated regions of the human prepronociceptin (hPPNOC) - enkephalin (hPPENK), dynorphin (hPPDYN) and opioimelanocortin (hPPOMC) genes.". Page 17, line 2 of the specification through page 18, line 11, further elaborates on Figure 7, noting that the "nucleotide sequence of the murine and human prepronociceptin (PPNOC) genes display organizational and structural features which are very similar to those genes encoding the precursors to endogenous opioid peptides, enkephalins (PPENK), dynorphins/neo-dynorphins (PPDYN) and β-endorphin (PPOMC)...". Therefore, the specification provides several working examples to use this invention.

Moreover, one with skill in the art would know how to use these related sequences to identify additional isolated peptides with 70% to 90% homology to the peptide encoded by SEQ ID NO: 1 or its complimentary strand. Page 17, line 26 to page 18, line 2 reveals that the "deduced amino acid sequence of prepronociceptin is highly conserved across murine and human species, especially the C-terminal quarter which hosts nociceptin itself. The N-terminal end of the precursor consists of a hydrophobic stretch of about 20 amino acids which may represent the

signal peptide necessary for translocation into the rough endoplasmic reticulum, followed by a cystein-rich portion which is also found in other hormone precursors, especially those to endogenous opioid peptides. Indeed, the pattern of cystein residues in pronociceptin is exactly the same as in proenkephalin and prodynorphin...". Page 18, lines 6-11 disclose the region of lowest homology across murine and human prepronociceptins, including "a variable number of acidic motifs". This provides one skilled in the art with guidance as to which regions of the peptide must be conserved, which regions can be deleted, and which regions can be mutated to still have an active ligand of the ORL_1 receptor.

Homologues of nociceptin are known in the art which have 70% to 90% homology and would have the function of "a ligand of the opioid receptor-like 1 (ORL_1) receptor". Known structural variants and derivatives of nociceptin which have either a similar or increased affinity for ORL_1 receptors exist in the art. These variants/derivatives of nociceptin fall under the definition of an isolated peptide encoded by a polynucleotide which corresponds to at least 70% or 90% of SEQ ID NO: 1 or its complimentary strand. Examples of these variants include truncated nociceptin, mono-substituted nociceptin, bi-substituted nociceptin and pseudopeptides derived from nociceptin. A copy of references containing these known structural variants and derivatives of nociceptin which have either a similar or increased affinity for ORL_1 receptors will be sent to the Examiner under separate cover. In addition, the specification provides guidance to one of skill in the art as to the regions of nociceptin which can be deleted, largely mutated, and conservatively mutated while still maintaining function as a ligand of ORL_1.

In summary, there is considerable enablement for one skilled in the art to identify an isolated peptide encoded by a polynucleotide which corresponds to at least 70% or 90% of SEQ ID NO: 1 or its complimentary strand.

Therefore, the Applicants respectfully request withdrawal of the rejection of Claims 35-36, 38 and 47 under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 35-42 and 47 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner believes that the recitation of the term "like" in Claims 35 and 40 is a relative term which renders the claim indefinite.

However, the term "like" is used as the specific name of a receptor, i.e. opioid receptor-like 1 (ORL_1). Therefore, one of skill in the art would have a clear understanding of the term "like" in this context. The opioid receptor-like 1 receptor is a specific receptor name that was characterized by the inventors in 1994. (Included in IDS: Mollereau *et al.* FEBS Lett. 1994. 341(1): 33-38.) It was named opioid receptor-like 1 to establish its relation, but distinction, to the opioid receptor family. The Applicants identified numerous journal articles in a search covering the period prior to the International filing date of the present application relating to the specific ORL_1 mentioned in both the specification and the claims. These articles indicate that one with skill in the art would identify the term ORL_1 and the use of the word "like" in that term as relating to a specific receptor that is well known in the art.

It is common in the art with numerous other receptors and growth factors to employ the same naming device when referring to something novel, but similar, to the established protein. For example, there is a calcitonin receptor-like receptor (CRLR), a cytokine receptor-like protein (CYRL), and a formyl peptide receptor-like 1 (FPRL1), just to name a few. They are not arbitrary protein names, but very specific, sequenced proteins.

Therefore, the Applicants respectfully request withdrawal of the rejection of Claims 35 and 40 under 35 U.S.C. §112, second paragraph. Claims 36-39, 41-42 and 47 were also rejected because of their dependency on the recitation of the term "like". Since the independent claims are allowable, the Applicants respectfully request withdrawal of the rejection for these claims, as well.

Conclusion

Should there be any questions concerning the application, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 20 Mar. 2001

By: Daniel Altman

Daniel E. Altman
Registration No. 34,115
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(949) 760-0404

O:\DOCS\MCM\MCM-1001.DOC
031901

VERSION WITH MARKINGS TO SHOW CHANGES MADE

35. **(Twice Amended)** An isolated polynucleotide which is at least 70% identical to SEQ ID NO: 1 or its complimentary strand wherein said polynucleotide encodes a ligand of the opioid receptor-**[type]**like 1 (ORL_1) receptor.

38. **(Twice Amended)** An isolated peptide encoded by an isolated polynucleotide which is at least 70 % identical to SEQ ID NO: 1 or its complimentary strand wherein said polynucleotide encodes a ligand of the opioid receptor-**[type]**like 1 (ORL_1) receptor.